

Bandolier **Extra**

Evidence-based health care

March 2005

TOPICAL ANALGESICS: A REVIEW OF REVIEWS AND A BIT OF PERSPECTIVE

Executive summary

This issue of Bandolier Extra pulls together the available evidence about topical analgesics. It covers analgesics that are rubbed onto the skin to produce pain relief, and will examine topical capsaicin, topical rubefaciants and topical NSAIDs. It will not cover topical local anaesthetics.

The facts are important for payers and prescribers. But they are also important for consumers. Topical analgesics are widely available without prescription, and widely advertised. Consumers need to have the best information available, as well. The evidence is that topical NSAIDs are effective and safe.

In this review, systematic reviews were sought for topical capsaicin, rubefaciants, and NSAIDs, in acute and chronic painful conditions. Reviews included only trials that were randomised, double blind, had more than 10 patients in each treatment arm, and had useable outcomes.

Topical capsaicin

Capsaicin studies were conducted in chronic neuropathic and musculoskeletal pain, at different strengths of cream in trials of eight weeks duration.

In neuropathic conditions in six trials (656 patients), topical capsaicin (0.075%) was better than placebo with an NNT of 5.7 (95% CI 4.0 to 10).

In musculoskeletal conditions in three trials (368 patients) topical capsaicin (0.025% or plaster) was better than placebo with an NNT of 8.1 (4.6 to 34).

About one third of patients experienced local adverse events with capsaicin, who would not have done so with placebo.

Topical rubefaciants

Rubefacient studies consisted entirely of topical salicylates in trials using one week outcomes for acute conditions and two week outcomes for chronic conditions.

In acute conditions in three trials with 182 patients topical salicylate was significantly better than placebo with an NNT of 2.1 (1.7 to 2.8).

In chronic conditions in six trials with 429 patients topical salicylate was significantly better than placebo with an NNT of 5.3 (CI 3.6 to 10.2), but the three larger, more valid studies were without significant effect.

Local adverse events and withdrawals were generally rare in trials that reported them.

Topical NSAIDs

Topical NSAIDs were well investigated in acute painful conditions, which were all musculoskeletal in nature, in trials using one week outcomes.

Topical NSAID was significantly better than placebo in 19 of the 26 trials, with a pooled relative benefit of 1.6 (1.4 to 1.7), and NNT of 3.8 (3.4 to 4.4) compared with placebo for the outcome of half pain relief at seven days. Ketoprofen was significantly better than all other topical NSAIDs.

Topical NSAIDs were well investigated in chronic painful conditions, which were all musculoskeletal in nature, in trials using two week outcomes.

Topical NSAIDs were clearly better than placebo in chronic musculoskeletal pain, with an NNT of 4.4 (3.6 to 5.6) in the best trials. Studies were generally of short duration, and no single preparation could be shown to be better than another. No study showed oral NSAID to be better than topical NSAID.

Local adverse events, systemic adverse events, or withdrawals due to an adverse event were rare, and no different between topical NSAID and placebo.

Comment

Using criteria of quality, validity, and size, the best evidence is for topical NSAIDs in acute conditions. Trials of one week were appropriate, and good efficacy was demonstrated. Topical NSAIDs in chronic conditions were limited by generally being of short duration compared to expected longer-term use.

Topical capsaicin trials were limited in size and validity, and demonstrated limited efficacy in neuropathic and musculoskeletal conditions. Evidence on topical rubefaciants was limited in quality, validity, and size. Better trials showed no difference from placebo. There is no good evidence that

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INTRODUCTION

This issue of *Bandolier Extra* pulls together the available, and growing, evidence about topical analgesics. It covers analgesics that are rubbed onto the skin to produce pain relief, and will examine topical capsaicin, topical rubefacients and topical NSAIDs. It will not cover topical local anaesthetics.

For all topical analgesics there is an element of unknown territory. The strongest evidence will come from systematic reviews and meta-analyses of randomised trials, where the three critical criteria of quality, validity, and size are met. It will be necessary to look at some of the underlying science, where it exists, in part to satisfy ourselves that there is a biological plausibility to topical analgesia, and that it isn't just the rubbing!

This is an area of considerable interest and controversy, despite topical analgesics having been around for many years. In some parts of the world topical analgesics are widely used and their effectiveness recognised. In others, topical analgesics are thought of as junk medicine, and any evidence for their efficacy dismissed. Use of topical analgesics is even occasionally used as a marker of bad prescribing. Some doctors get their earnings docked for prescribing them, or are bribed by their employers not to use them, irrespective of evidence. These interesting ethical issues are not examined here: this *Bandolier Extra* will stick to the facts.

The facts are important for payers and prescribers. But they are also important for consumers. Topical analgesics are widely available without prescription, and widely advertised. Consumers need to have the best information available, as well.

Definitions

The first thing needed is a classification of topical analgesics. The problem we face is that of a number of possible definitions for rubefacients and NSAIDs, capsaicin and local anaesthetics. The dimensions are:

- ◆ Molecular structure and pharmacology. Some compounds, like salicylates, are related pharmacologically to aspirin and NSAIDs, but in the form that they are often used in topical products (often as amine derivatives) their principal action is to act as skin irritants (called counter irritants in many texts, to 'counter' pain). By contrast topical NSAIDs act by penetrating deep into underlying structures to inhibit cyclooxygenase enzymes responsible for development of inflammatory processes.
- ◆ Concentration. The concentration of components of topical analgesics varies considerably, and the dose-response relationships are largely unknown. For some agents, like capsaicin, concentration may define prescription or OTC (over-the-counter, no prescription needed) status.
- ◆ A number of products contain several agents that may or may not be active in one or other ways.
- ◆ Availability with or without prescription.
- ◆ Different definitions are used. For instance, PACT (UK

prescribing data) combines "rubefacients and other topical anti-rheumatics" and includes topical nonsteroidal drugs, and thus mirrors the definition of the BNF (British National Formulary). The BNF defines the properties of a rubefacient, without defining what a rubefacient actually is, so our definition here is that "rubefacients act by counter-irritation".

- ◆ The Royal Society of Medicine gives a definition thus: "Agents are also called counter-irritant. The name derives from the fact that these agents cause a reddening of the skin by causing the blood vessels of the skin to dilate, which gives a soothing feeling of warmth. The term counter-irritant refers to the idea that irritation of the sensory nerve endings alters or offsets pain in the underlying muscle or joints that are served by the same nerves. See capsaicin; capsicum oleoresin; choline salicylate; ethyl salicylate; glycol salicylate; methyl salicylate; menthol; salicylic acid; turpentine oil."

The *Pharmaceutical Journal* helpfully distinguishes three main categories of topical analgesics:

- ◆ Rubefacients: traditional formulations based on salicylate and nicotinate esters, capsaicin and capsicum extracts and derivatives.
- ◆ NSAIDs: diclofenac, felbinac, ibuprofen, ketoprofen, piroxicam, naproxen, flurbiprofen and other NSAIDs.
- ◆ A miscellaneous group: including benzydamine, mucopolysaccharide polysulphate, salicylamide and cooling sprays.

This review examines the rubefacients and NSAIDs as defined above, together with prescription-strength capsaicin. *Bandolier* therefore sought reviews of:

- ◆ Topical capsaicin in chronic pain conditions. Our prior definition here is based on concentration, prescription status, on being a single active agent, and possibly on mode of action.
- ◆ Topical rubefacients in acute and chronic pain states (but not stings or sunburn), and to include all salicylate products. The intention will be to include all products listed as rubefacients or counter irritants by Martindale, but with a prior intent to perform a sensitivity analysis for salicylates alone, and other products alone where there are sufficient trials or numbers of patients in a given pain condition. *Movelat* contains salicylic acid, though its status is as a heparinoid. Again, a sensitivity analysis for this product alone is planned.
- ◆ Topical NSAIDs in acute pain conditions, like strains and sprains.
- ◆ Topical NSAIDs in chronic pain conditions, like arthritis.

Capsaicin

In the UK, capsaicin cream is available at strengths of 0.075% for neuropathic pain, and 0.025% for musculoskeletal pain, and that separation of strength and condition seems to have been respected in clinical trials.

Table 1: Definitions and uses of some rubefacients

Glucosamine sulphate	Given in the treatment of rheumatic disorders
Chondroitin sulphate	No comments
Camphor	Applied externally, camphor acts as a rubefacient and mild analgesic
Peppermint oil	No comments
Hydroxyethylsalicylate	(2- Hydroxyethylsalicylate or glycol salicylate) salicylic acid derivative used in topical rubefacient preparations
Escin	from horse chestnut; mixture of saponins
Diethylamine salicylate	Salicylic acid derivative used topically in rubefacient preparations
Copper salicylate	No comments
Comfrey	Comfrey has been applied topically in the treatment of inflammatory disorders
Poison ivy	Contain irritant poisons
Marsh tea	No comments
Triethylamine salicylate	Same as triethalonamine salicylate and trolamine salicylate
Copper salicylate	No comments
Trolamine salicylate	salicylic acid derivative used in topical rubefacient preparations
Benzydamine	No comments
Bezydamine hydrochloride	NSAID
Benzydamine salicylate	No comments
Salicylic acid	Mild irritant
Dexpanthenol	(pantothenic acid analogue) No accepted therapeutic uses in human medicine
Heparin	Anticoagulant and found in topical preps for various inflammatory disorders
Dimethylsulphoxide	(DMSO) exceptional solvent properties. Anti-inflammatory & vasodilatory properties
Movelat (prep)	Heparinoid containing salicylic acid
Intralgin (prep)	Benzocaine & salicylamide
Benzocaine	Local anaesthetic
Salicylamide	Salicylic acid derivative applied topically in rubefacient preparations
Salonpas (prep)	Methyl salicylate, menthol, camphor, benzyl nicotinate, glycol salicylate
Methyl salicylate	Salicylic acid derivative irritant to the skin and is used in rubefacient preparations
Menthol	Vasodilation causing sensation of coldness followed by analgesic effect
Benzyl nicotinate	Used topically in rubefacient preparations

Rubefacients

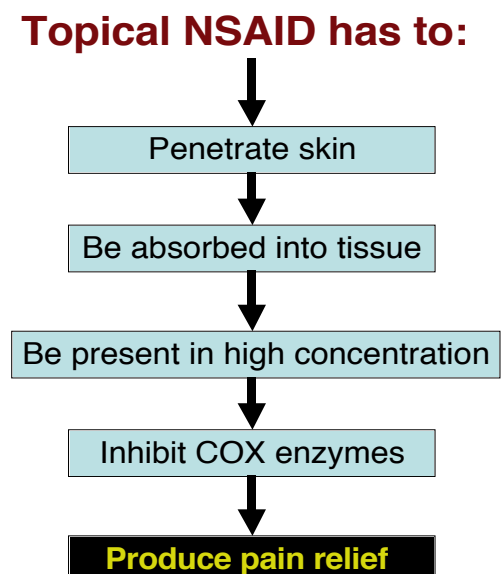
This has a special complexity because of the number of different chemicals that can be a rubefacient. Definitions according to Martindale are shown in Table 1.

Topical NSAIDs

Topical NSAIDs for pain relief remain one of the more controversial subjects in analgesic practice. In some parts of the world their use is regarded as sensible, with adequate evidence for their use. In other parts of the world they are regarded as little more than placebo, with any effect due just to the rubbing. In yet others, their use is almost unknown.

This will be about more than just their efficacy in clinical trials, because to fully appreciate the evidence information will be required about skin penetration, tissue concentrations, and blood levels, particularly to demonstrate differences between oral and topical administration (Figure 1).

Figure 1: Evidence needed for topical NSAIDs



TOPICAL CAPSAICIN FOR CHRONIC PAIN

The information on topical capsaicin comes from a 2004 systematic review [1], updating a previous systematic review [2]. Changes from the previous systematic review include addition of newer studies, omission of studies that were duplicates, and limitation to neuropathic and musculoskeletal pain.

Clinical bottom line

In neuropathic conditions in six trials (656 patients), topical capsaicin (0.075%) was better than placebo with an NNT of 5.7 (95% CI 4.0 to 10).

In musculoskeletal conditions in three trials (368 patients) topical capsaicin (0.025% or plaster) was better than placebo with an NNT of 8.1 (4.6 to 34).

About one third of patients experienced local adverse events with capsaicin, who would not have done so with placebo.

Background

Capsaicin is the active compound present in chilli peppers, responsible for making them hot when eaten. It binds to nociceptors in the skin, causing an initial excitation of the neurones and a period of enhanced sensitivity to noxious stimuli, usually perceived as itching, pricking or burning sensations. This is followed by a refractory period with reduced sensitivity and, after repeated applications, persistent desensitisation. It is the ability of capsaicin to desensitise nociceptors that is exploited for therapeutic pain relief.

For post-herpetic neuralgia and diabetic neuropathy, treatment is with 0.075% cream three to four times daily for eight weeks (followed by review) and for osteoarthritis treatment is with 0.025% cream, four times daily. Capsaicin is available in the UK on prescription only, but may be present in small quantities in topical rubefacients sold through pharmacies. According to the Prescription Cost Analysis, there were over 120 000 prescriptions for topical capsaicin in England in 2002, at a total cost of £2.2 million, out of a total of 4.5 million prescriptions for rubefacients and other topical anti-rheumatic drugs.

Systematic review

Extensive searches looked for randomised and double-blind, active or placebo-controlled trials, in adult patients experiencing chronic pain from either neuropathic (diabetic neuropathy, postherpetic neuralgia, polyneuropathy other neuropathies or chronic post-operative pain) or musculoskeletal (arthritic disorders, back pain, other chronic muscle pain or fibromyalgia) disorders. Application of treatment had to be 3-4 times daily, in accordance with manufacturers' instructions, and at least ten patients had to be randomised to each treatment group.

- Date review completed: March 2003
- Number of trials included: 16
- Number of patients: 1556
- Control groups: Placebo or active controls
- Main outcomes: Clinical success, representing approximately a 50% reduction in pain, using a hierarchy of outcomes. Outcomes closest to four weeks (minimum three weeks) were extracted in musculoskeletal conditions, and closest to eight weeks (minimum six weeks) in neuropathic conditions.

Results

Trials scored highly on a scales of quality of reporting, and of validity in pain. Fourteen of 16 trials scored 3 points or more out of five for reporting quality (minimising bias). Trial validity scores ranged between nine and 14 on a scale from zero to 16 (scores of 9 or above minimise bias). Capsaicin was significantly better than placebo for neuropathic and musculoskeletal pain, though with wide dispersion in results of individual (small) trials (Figure 2).

Neuropathic pain

Results in neuropathic pain at four and eight weeks are shown in Table 2. The mean treatment response at eight weeks was 60%, while the response to placebo was 42%. The NNT compared to placebo at eight weeks was 5.7 (4.0 to 10).

Musculoskeletal pain

Results in musculoskeletal pain at four weeks are shown in Table 2. The mean treatment response at four weeks was 38%, while the response to placebo was 25%. The NNT compared to placebo at eight weeks was 8.1 (4.6 to 34).

Figure 2: Trials of topical capsaicin in musculoskeletal (dark) and neuropathic pain (light)
Success with capsaicin (%)

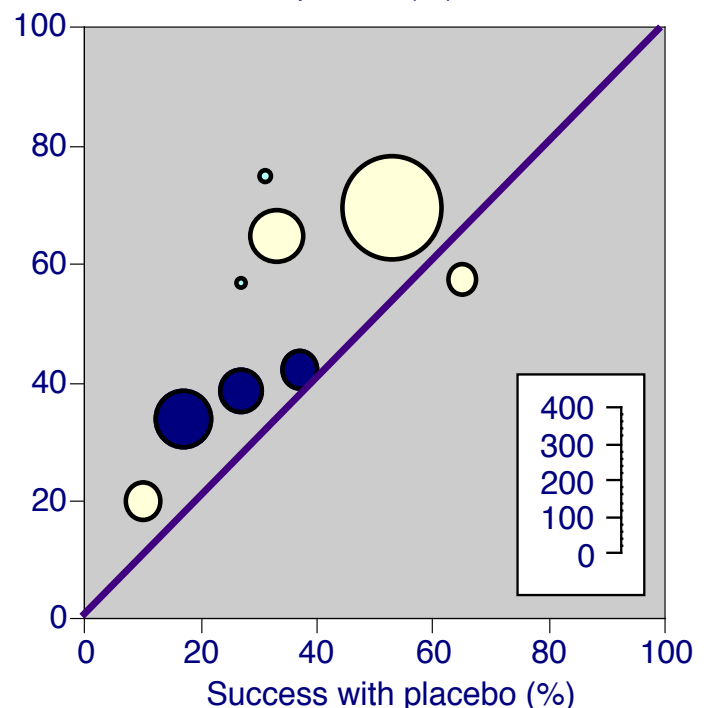


Table 2: Results for topical capsaicin in chronic pain

EFFICACY	Trials	Patients	Success with		Relative benefit (95% CI)	NNT (95% CI)
			Topical capsaicin	Topical placebo		
neuropathic pain						
efficacy at 4 weeks	4	313	91/159	64/154	1.4 (1.1 to 1.7)	6.4 (3.8 to 21)
efficacy at 8 weeks	6	656	197/331	136/325	1.4 (1.2 to 1.7)	5.7 (4.0 to 10)
musculoskeletal pain						
efficacy at 4 weeks	3	368	70/186	46/182	1.5 (1.1 to 2.0)	8.1 (4.6 to 34)
HARM					Relative risk (95% CI)	NNH (95% CI)
musculoskeletal pain						
local AE at 4 weeks	3	190	48/98	9/92	5.0 (2.6 to 9.6)	2.6 (2.0 to 3.6)
AE related withdrawals at 4 weeks	4	398	19/203	6/195	2.5 (1.1 to 5.6)	16.0 (9.1 to 63)
neuropathic pain						
local AE at 8 weeks	4	300	89/154	26/146	3.2 (2.2 to 4.6)	2.5 (2.0 to 3.3)
AE related withdrawals at 8 weeks	5	503	40/253	6/250	5.5 (2.6 to 12)	7.5 (5.5 to 12)
combined						
local AE	7	490	137/252	35/238	3.6 (2.6 to 5.0)	2.5 (2.1 to 3.1)
AE related withdrawals	9	901	59/456	12/445	4.0 (2.3 to 6.8)	9.8 (7.3 to 15)

Adverse events

Local adverse events occurred more frequently with capsaicin cream than with placebo, with a number needed to harm of 2.5 (2.1 to 15). Over half (54%) of patients had a local adverse event with capsaicin creams, and 13% of patients withdrew because of adverse events. Coughing was reported in 29/372 (8%) patients treated with capsaicin 0.075%, but in none of the placebo-controlled trials using 0.025% capsaicin.

Comment

Topical capsaicin can be distinguished from placebo in both neuropathic pain and in musculoskeletal pain. The quality and validity of the trials were high, and those in neuropathic pain were of reasonable duration, at eight weeks.

However, estimates of efficacy are low in musculoskeletal pain, and adverse event rates high, with limited patient numbers. Topical capsaicin is an unlikely first or even second choice for treatment, but will help some people.

TOPICAL SALICYLATE (RUBEFACIENT) FOR ACUTE AND CHRONIC PAIN

The information on topical salicylate comes from a 2004 systematic review [3], updating a previous systematic review in which topical salicylate was included with topical NSAIDs [4]. Changes from the previous systematic review include addition of newer studies and separate analysis for salicylates. No trials for other topical rubefacients were found.

Clinical bottom line

In acute conditions in three trials with 182 patients topical salicylate was significantly better than placebo with an NNT of 2.1 (1.7 to 2.8).

In chronic conditions in six trials with 429 patients topical salicylate was significantly better than placebo with an NNT of 5.3 (CI 3.6 to 10.2), but the three larger, more valid studies were without significant effect.

Local adverse events and withdrawals were generally rare in trials that reported them.

Background

Rubefacients are believed to work by counter-irritation, to relieve pain in the muscles, joints and tendons and in non-articular musculoskeletal conditions, rather than as NSAIDs that inhibit cyclo-oxygenase responsible for prostaglandin biosynthesis and the development of inflammation. Rubefacients are usually used as adjuvants to other therapies, such as oral analgesics, support bandages, rest, ice and compression, and may be particularly useful for patients who cannot tolerate the adverse events associated with some oral analgesics.

Systematic review

Extensive searches looked for randomised, active or placebo-controlled trials in adult patients experiencing either acute (sprains, strains and sports injuries) or chronic (arthritis, musculoskeletal) pain.

- Date review completed: March 2003
- Number of trials included: 12, three of which had active controls
- Number of patients: 862
- Control groups: placebo or active controls
- Main outcomes: Clinical success, representing approximately a 50% reduction in pain, using a hierarchy of outcomes. Outcomes closest to seven days (but at least three days) were required for acute conditions, and closest to 14 days (but at least seven days) for chronic conditions.

Results

Included trials had quality scores ranging between two and four, and all were randomised and double blind. Eleven of the 14 studies had quality scores of 3 or more out of five (minimising bias), and six of the 14 studies had validity scores of 9 or more (minimising bias).

Acute pain

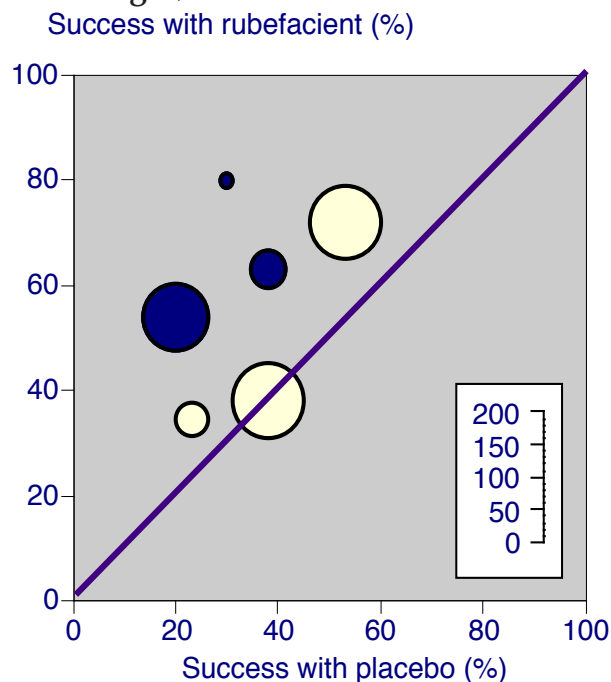
Three placebo controlled trials (one of low validity) had information from 182 patients. The mean percentage of patients with at least 50% pain relief was 67% with topical salicylate and 18% with placebo. Treatment with rubefacient was significantly better than placebo with an NNT of 2.1 (1.7 to 2.8) for at least 50% pain relief at seven days in acute conditions compared with placebo (Table 3).

Chronic pain

Six placebo controlled trials (three of low validity) had information on 429 comparisons from 403 patients (Figure 3). The mean percentage of patients with at least 50% pain relief was 54% with topical salicylate and 36% with placebo. Treatment with rubefacient was significantly better than placebo with an NNT of 5.3 (3.6 to 10) for at least 50% pain relief at 14 days in acute conditions compared with placebo (Table 3).

Better trials had less effect. For the three trials of higher validity, there was no difference between topical salicylate and placebo (Table 3).

Figure 3: Trials of topical salicylate in chronic pain (low validity scores dark, high validity scores light)



Adverse events

Adverse event reporting was poor, but few were reported.

Comment

The evidence for efficacy of topical salicylates was poor. There were only two acute pain studies with decent validity scores, and only three in chronic pain. Valid chronic pain studies showed no difference between topical salicylate and placebo, while the acute pain studies could have been overturned if any negative studies emerged.

TOPICAL NSAIDS

For topical NSAIDs there is more information on background biology. That information allows us to investigate the evidence needed for topical NSAIDs (Figure 1). That evidence is presented here as skin penetration, plasma and

Table 3: Topical salicylates in acute and chronic pain

Condition	Trials	Patients	Success with		Relative benefit (95% CI)	NNT (95% CI)
			Topical salicylate	Topical placebo		
acute pain						
efficacy (all trials)	3	182	60/90	17/92	3.6 (2.4 to 5.6)	2.1 (1.7 to 2.8)
local AE	5	418	4/208	4/210	1.1 (0.4 to 3.5)	not significant
chronic pain						
efficacy (all trials)	6	429	125/230	80/225	1.5 (1.3 to 1.9)	5.3 (3.6 to 10.2)
validity score						
8 or less	3	176	55/92	22/84	2.2 (1.5 to 3.3)	3.0 (2.1 to 5.0)

Table 4: Selected experimental results on NSAID penetration of skin

Reference	Design	Results
Hadgraft et al. Skin Pharmacol Appl Skin Physiol 2003 16: 137-142	Human skin samples used as permeation barrier to ibuprofen preparations, and permeation of ibuprofen measured over 48 hours at 37 C	Mean absorption was between 4% and 25%, linearly over 48 hours. Ibuspray, Ibugel and Ibumousse best.
Escribano et al. Europ J Pharm Sci 2003 19: 203-210	Human skin samples used as permeation barrier to diclofenac preparations, and permeation of diclofenac measured over 24 hours at 32 C	Permeated amount varied depending on formulation, with some formulations much better than others
Sloan & Wasdo. Med Res Rev 2003 23: 763-793	Review and theoretical approach to transdermal drug delivery	Indicates that balance between lipid and aqueous solubility is needed to optimise permeation, and that use of prodrug esters of NSAIDs could enhance dermal penetration
Paolino et al. Int J Pharm 2002 244: 21-31	Human skin samples used as permeation barrier to ketoprofen preparations, and permeation of ketoprofen measured over 24 hours	Microemulsions showed enhanced permeation of ketoprofen compared with creams. Microemulsions were better than gels, which were better than creams
Montastier et al. Med du Sport 1994 68: 40-42	Diffusion across an artificial membrane	Ketoprofen had much better penetration, with 22% released compared with 11% diclofenac, 4% niflumic acid, 1% piroxicam

tissue levels of NSAIDs after topical application, comparison with oral NSAID, and results of updated systematic reviews of topical NSAIDs in acute and chronic pain.

1 PENETRATING THE SKIN

Clinical bottom line

In vitro studies and theoretical considerations indicate that NSAIDs could be effective when applied topically. Formulation is crucial to good skin penetration. Diclofenac, ketorolac, and ketoprofen are good candidates on theoretical grounds.

Background

For topical NSAIDs to be effective, they have to at least penetrate the skin. Only when the drug has entered the lower layers of the skin can it be absorbed by blood and transported to the site of action, or penetrate deeper into areas where inflammation occurs.

There are two ways of answering this question. In volunteers or patients we can measure drug levels in the blood or underlying tissues. Another method is to use experimental systems to investigate how different drugs pass through skin.

Experimental design

These latter experiments tend to be conducted in a similar manner. A device with two chambers is used, in which the chambers are separated by either an artificial membrane or a piece of human skin removed at operation. Typically only the epidermis is used.

Drug can either be placed on the outer surface of the skin, or kept in solution in high concentration in one chamber, and samples removed at intervals from the other chamber, and drug concentrations measured. Drug should move from high to low concentration. The more difficult the barrier is to penetrate, the slower the diffusion, and the easier it is to penetrate, the faster the diffusion.

Diffusion depends on several factors, and these will include the skin or membrane itself, the drug, and any other materials that are used either to increase or decrease diffusion.

Experimental results

Selected experimental results are shown in Table 4. Reading these and other studies demonstrates various features of drug penetration:

- 1 Importance of the drug. Theoretical and experimental results suggest that a balance between lipid and aqueous solubility is needed to optimise penetration. Use of prodrug esters has been suggested as a way of enhancing permeability [5].
- 2 Importance of formulation. Several studies (Table 4) indicated that formulation can make a huge difference in drug permeation. Creams are generally less effective than gels or sprays, but newer formulations like microemulsions have greater potential.

Theoretical considerations

For a topical NSAID to be effective, it has not only to reach inflamed tissue, but also to be there in sufficient concentration to produce a relevant anti-inflammatory activity. The

ratio of these two factors has been called an index of topical anti-inflammatory activity [6].

Theoretical considerations indicate that four drugs are particularly good candidates, diclofenac, ketorolac, ketoprofen and indomethacin might be good candidates, while piroxicam and tenoxicam are not (ibuprofen was not tested). It is interesting to compare this theoretical approach to results from use of topical NSAIDs for strains and sprains, where indirect comparison suggests that ketoprofen and ibuprofen had the best activity, while piroxicam and indomethacin had the worst.

Comment

In vitro studies and theoretical considerations indicate that NSAIDs could be effective when applied topically. Formulation is crucial to good skin penetration.

2 PLASMA AND TISSUE CONCENTRATIONS

Clinical bottom line

Topical NSAID administration results in peak plasma concentrations that are much lower than after oral administration of standard NSAID doses. Plasma concentrations after topical administration are generally less than 5% of those in plasma.

Synovial fluid concentrations are also lower, but concentrations in meniscus or cartilage are 4-7 times higher than after oral administration.

Concentrations in tendon sheath are several hundred times greater than plasma concentrations after topical administration.

Plasma

Ibuprofen

Plasma concentrations after topical administration are generally low. Studies that have measured plasma concentrations, after single or multiple applications, generally find concentrations to be below about 500 ng/mL (Table 5). The exception was one study in six volunteers with a single application of one of three ibuprofen preparations, in which the mean plasma concentration was about 1,400 ng/mL. For the two other preparations the maximum plasma concentrations were much lower, less than 400 ng/mL.

These concentrations are very much lower than peak concentrations with oral ibuprofen at usual doses of about 400 mg, where peak concentrations are generally above 20,000 ng/mL (20 µg/mL).

Ketoprofen

For ketoprofen, plasma concentrations after a single application were generally below 50 ng/mL and after multiple applications were about 150-200 ng/mL (Table 5). In a detailed study of single and multiple applications of ketoprofen in a

Figure 4: Plasma kinetics of ketoprofen after first and last doses of topical application

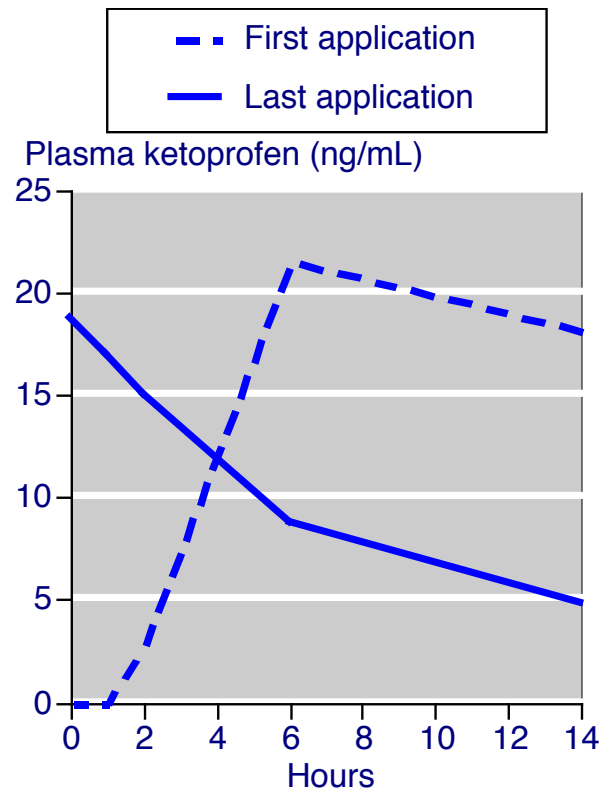
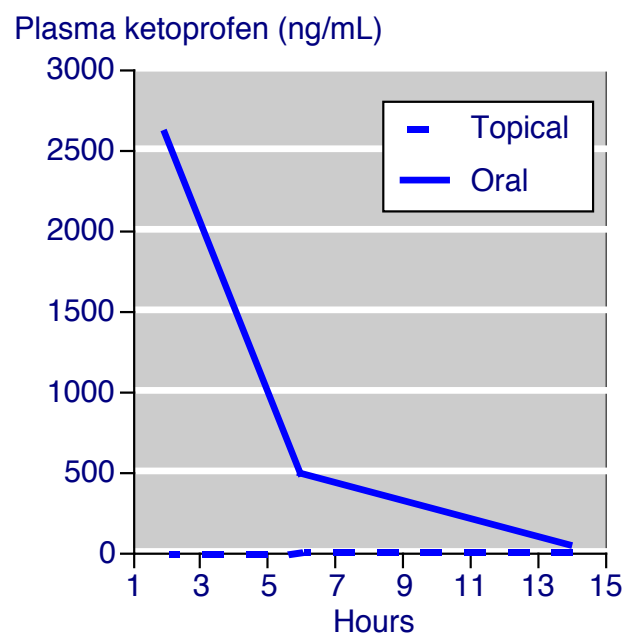


Figure 5: Plasma kinetics of ketoprofen after topical and oral administration



large number of patients [7], mean plasma concentrations were no higher than about 20 ng/mL (Figure 4). These levels were achieved within six hours of the first application, but fell away rapidly after the last application was removed, following five days of multiple applications.

After oral ketoprofen, peak plasma concentrations were at least two orders of magnitude higher, at 2,600 ng/mL two hours after a single 50 mg dose, and were at least twice as high as the maximum value after topical application even 14 hours after an oral dose (Figure 5).

Table 5: Plasma and tissue concentrations after topical NSAID application

Reference	Design	Results
Plasma and tissue concentrations		
Cagnie et al. Physical Therapy 2003 83: 707-712	26 patients undergoing knee arthroscopy used 2.5% ketoprofen cream with and without ultrasound for 5 minutes 47-77 minutes before arthroscopy. Synovial tissue and a blood sample 2 hours after topical administration were collected	Plasma levels below 4 ng/mL in most patients Synovial tissue 2 µg/g without ultrasound, but about 20-30 µg/g with ultrasound, with wide variation
Osterwalder et al. Arzneimittel-Forsch 2002 52: 822-827	10 patients undergoing knee arthroscopy or carpal tunnel release treated with ketoprofen patch 6 days before surgery. Tissue and blood samples were collected	Plasma concentration 13-112 ng/mL Synovial tissue 20-430 ng/g Tendon sheath 13-32 µg/g
Tegeger et al. Pharm Res 2001 18: 980-986	8 volunteers given single dose 100 mg ketoprofen topically. Tissue dialysis and blood samples taken	Plasma levels 10-50 ng/mL by 8 hours Muscle and subcutaneous tissue below 20 ng/mL
Tedeger et al. Clin Pharmacol Ther 1999 65: 357-368	11 volunteers given single dose 800 mg oral ibuprofen or 16 g 5% ibuprofen gel. Tissue dialysis and blood samples taken	Higher subcutaneous tissue dialysate concentrations and similar muscle dialysate concentrations with topical compared with oral
Rolf et al. Rheumatology 1999 38: 564-567	100 patients with knee disorders requiring arthroscopy. Single application topical ketoprofen in 40, multiple applications for 5 days in 30, or single dose 50 mg oral ketoprofen	Higher concentrations in plasma, synovial fluid and synovial tissue after oral than topical, but higher levels in meniscus and cartilage for topical than oral administration
Dominkus et al. Arzneimittel-Forsch 1996 46: 1138-1142	17 patients with degenerative knee disorders given 1200 mg oral ibuprofen daily or topical ibuprofen daily for 3 days. Blood and synovial fluid samples taken	Topical administration produced higher concentrations in fasciae, muscle and subcutaneous tissue than in plasma. Concentrations of ibuprofen were in therapeutically effective levels 15 hours after topical or oral administration
Gallacchi & Marcolongo. Drugs Expt Clin Res 1993 XIX: 97-100	8 patients with knee joint effusion used diclofenac plasters for 4 days. Blood samples and synovial fluid samples collected	After four days max plasma concentration of diclofenac was 3.6 ng/mL, and synovial fluid concentration 1 ng/mL
Radermacher et al. Br J Clin Pharmacol 1991 31: 537-541	10 patients with bilateral knee effusion treated with diclofenac gel for 3 days. Randomised double-blind to active or control on different knees. Blood and synovial fluid samples collected.	Plasma concentration of diclofenac about 40 ng/mL Synovial fluid 26 ng/mL in treated and 22 ng/mL in untreated knee
Berner et al. Drugs Expt Clin Res 1989 XV: 559-564	10 volunteers and 8 patients with OA knee had either a single application ibuprofen or 3 times daily ibuprofen for 3 days. Blood and tissue samples collected as appropriate.	In volunteers, plasma ibuprofen was 100-200 ng/mL Patients had end of study blood concentration of 90 ng/mL Tissue concentrations were 7 µg/g in capsule, 9 µg/g in tendon and 20 µg/g in muscle
Ballerini et al. Int J Clin Pharm Res 1986 VI: 69-72	6 patients had ketoprofen gel applied daily for 3 days before operation, with 12 hours before operation. Blood, synovial fluid, and capsule samples taken	Plasma concentrations of ketoprofen about 18 ng/mL Synovial fluid 1,300 ng/mL Capsule 2.4 µg/g
Plasma concentrations		
Cannavino et al. Clin J Sports Med 2003 13: 200-208	32 men performing exercise to produce delayed action muscle soreness. Randomly assigned to topical ketoprofen or placebo to either or both legs. Pain scores and plasma concentrations	Significant reduction in muscle soreness with ketoprofen. Plasma concentrations in range of 23-53 ng/mL
Steen et al. Eur J Pain 2000 4: 195-209	19 volunteers in two studies of experimental cutaneous or muscle pain treated with topical or oral ibuprofen in randomised, double blind studies. Pain scores and plasma concentrations	Pain effectively treated with ibuprofen with both routes. After 800 mg oral ibuprofen, plasma concentrations were 13-25 µg/mL 30-90 minutes after dose. With application of 5% topical ibuprofen gel plasma concentrations were 43-62 ng/mL 45-90 minutes after dose.
Seth. Arzneimittel-Forsch 1993 43: 919-921	6 volunteers randomised to cross over with single application of ibuprofen preparations one week apart. Blood samples taken	Mean maximum plasma concentrations were: gel 1,400 ng/mL ointment 280 ng/mL cream 390 ng/mL
Seth. Arzneimittel-Forsch 1992 42: 120-122	7 volunteers randomised to cross over with single application of diclofenac preparations one week apart, and IM diclofenac 25 mg. Blood samples taken	Mean maximum plasma concentrations were: emulsion 1: 81 ng/mL emulsion 2: 39 ng/mL IM: 900 ng/mL
van den Ouweland et al. Eur J Clin Pharmacol 1989 36: 209-211	15 volunteers given single application of 10% and 5% naproxen gel. Blood samples taken	Maximum plasma concentrations were: 10% gel 40 ng/mL at 24 hours 5% gel 42 ng/mL at 48 hours
Flouvat et al. Arzneimittel-Forsch 1989 39: 812-815	10 volunteers used topical ketoprofen twice a day for 10 days. Blood samples taken.	Mean plasma concentrations were about 150-200 ng/mL after 10 days, and peak was 144 ng/mL after first administration

Diclofenac

Topical diclofenac produced maximum concentrations in plasma of 4-80 ng/mL after single or multiple applications (Table 5).

Synovial fluid

Synovial fluid concentrations of NSAIDs after topical application were generally lower than those found in plasma. The largest study [7] of ketoprofen found that the ratio of synovial fluid to plasma concentration was of the order of 0.6 to 0.8 at most times after the first or last dose.

Other tissues

Concentrations of NSAID in tissue after topical administration tended to be higher. For instance, after three days of application of topical ketoprofen, concentrations in the knee capsule were 2.4 µg/g, and after three days of topical ibuprofen were 7-9 µg/g in capsule and tendon. After a single dose, other studies found concentrations about a thousand-fold higher than plasma concentrations in subcutaneous tissue, muscle, and tendon sheath.

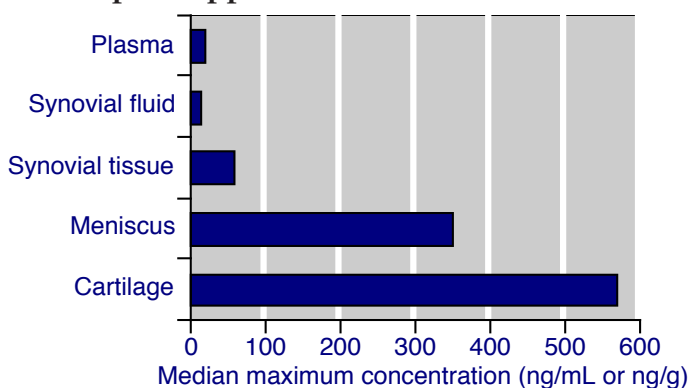
In the largest single study [7], very high concentrations of ketoprofen were found in meniscus and cartilage after topical administration, about 4-7 times greater than were found after oral administration, despite lower plasma concentrations (Figure 6).

Comment

This brief review confirms the view of others [8], that the maximum plasma values found after topical administration of NSAIDs are a small fraction of those expected after usual oral doses of the same NSAID. These low systemic concentrations probably account for the low occurrence of gastrointestinal adverse events with topical NSAIDs.

As best we can tell, synovial fluid concentrations are likely to reflect blood concentrations because this is a highly vascularised compartment. For instance, when topical diclofenac was applied to one knee in a randomised and double blind trial [9], the concentration of diclofenac in the untreated knee was almost the same as that in the treated knee.

Figure 6: Tissue concentrations of ketoprofen after topical application



However, concentrations of NSAID in tissue, particularly meniscus and cartilage, were very much higher after topical than oral administration, indicating that direct absorption through the skin into tissues of the joint does occur.

3 ORAL NSAID PHARMACOKINETICS

Topical NSAID kinetics and use have to be compared with oral administration, which is how NSAIDs are most often used. This, therefore, is a brief update on the pharmacokinetics of oral NSAIDs.

Clinical bottom line

After oral administration of NSAIDs, peak concentrations in plasma occur after about 1-2 hours, and then decline rapidly. Synovial fluid concentrations are similar to plasma concentrations after about four hours.

Plasma

Oral NSAIDs are rapidly absorbed. A review of ibuprofen kinetics shows that plasma concentrations after a single oral dose of 400 mg of ibuprofen the peak concentration were 20-40 µg/mL within 1-2 hours, but that six hours after administration the concentration was about 5µg/mL [10,11].

Synovial fluid

Synovial fluid concentrations are slower to reach maximum concentrations, which occur after 3-6 hours. Thereafter synovial fluid concentrations tend to be somewhat higher than in plasma, even up to 12 hours later. The time taken for plasma and synovial fluid concentrations to equilibrate has been shown to correlate with plasma half-life for the NSAIDs [11]. For aspirin it is under an hour, and for most common NSAIDs it is of the order of three to seven hours.

Table 6 shows results from some selected studies for ibuprofen, indomethacin and ketoprofen. Indomethacin and ketoprofen have lower peak plasma concentrations than ibuprofen, though synovial fluid concentrations had similar concentrations to plasma. A large recent study [7] showed that the synovial fluid and plasma concentrations of ketoprofen were similar by six hours after a single oral dose of 50 mg (Figure 7).

Other tissues

Maximum concentrations of ketoprofen in various tissues are shown in Figure 8. Concentrations of ketoprofen in meniscus and cartilage were well below those of synovial fluid and synovial tissue.

Comment

There are no surprises here. Oral NSAIDs are expected to be rapidly absorbed, and experience shows that they all have significant analgesic effects over a few hours in most pain states. In acute pain oral NSAIDs are highly effective, with low NNT values.

Table 6: Selected studies of oral kinetics of NSAIDs - plasma and tissue concentrations

Reference	Design	Results
Rolf et al. Rheumatology 1999 38: 564-567	100 patients with knee disorders requiring arthroscopy. Single application topical ketoprofen in 40, multiple applications for oral administration 5 days in 30, or single dose 50 mg oral ketoprofen	Mean plasma maximum concentration 2.5 $\mu\text{g/mL}$, and synovial fluid 0.35 $\mu\text{g/mL}$ after
Whitlan et al. Clin Pharmacol Ther 1981 29: 487-492.	15 patients with arthritis given 1200 mg ibuprofen daily for two days. Blood and synovial fluid samples taken	Mean serum ibuprofen concentration 20 $\mu\text{g/mL}$ Mean synovial fluid concentration 7.5 $\mu\text{g/L}$
Glass & Swannell. Br J Clin Pharmacol 1978 6:453P-454P	21 patients with osteo- or rheumatoid arthritis after single dose of 400 mg ibuprofen. Blood and synovial fluid samples taken	Peak serum ibuprofen 20-60 $\mu\text{g/mL}$ at 60-120 minutes, declined to below 10 $\mu\text{g/mL}$ after 240 minutes. Synovial fluid ibuprofen rose to about 10 $\mu\text{g/mL}$ by 240 minutes
Emori et al. Ann Rheum Dis. 1973 32: 433-435	7 patients with rheumatoid arthritis and chronic knee effusions given 50 mg indomethacin. Blood and synovial fluid samples taken	Peak serum indomethacin about 3 $\mu\text{g/mL}$ at one hour, falling below 0.5 $\mu\text{g/mL}$ by 4 hours Synovial fluid concentration at about 0.5 $\mu\text{g/mL}$ by 2 hours, declining slowly with plasma concentration

Figure 7: Plasma and synovial fluid kinetics of oral ketoprofen

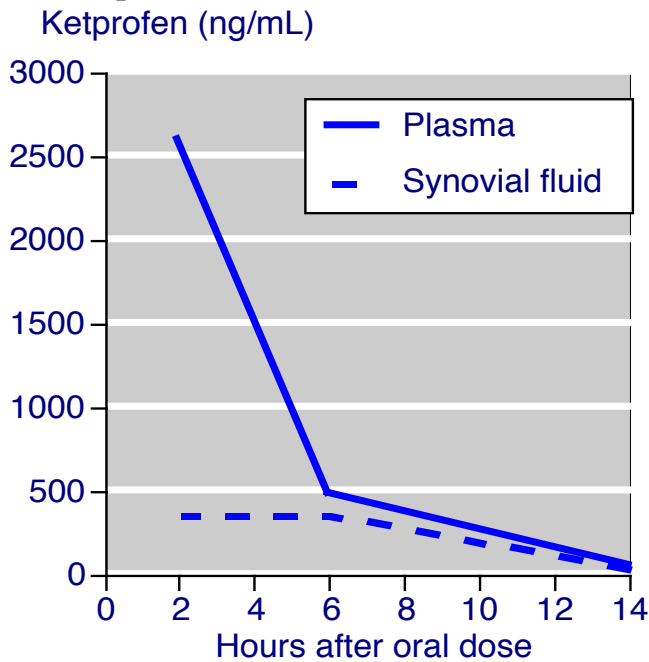


Figure 8: Median maximum concentrations of ketoprofen in tissue after oral administration

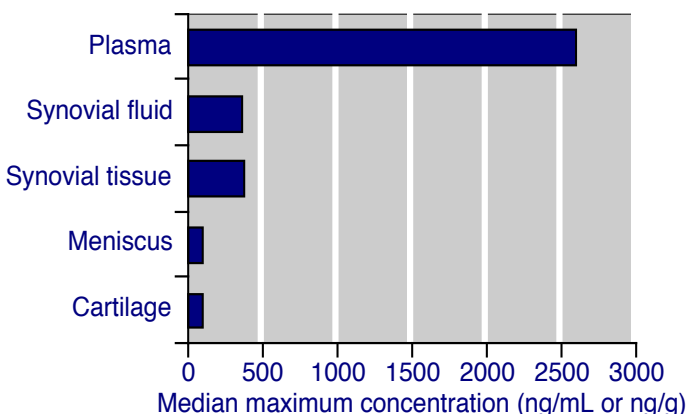
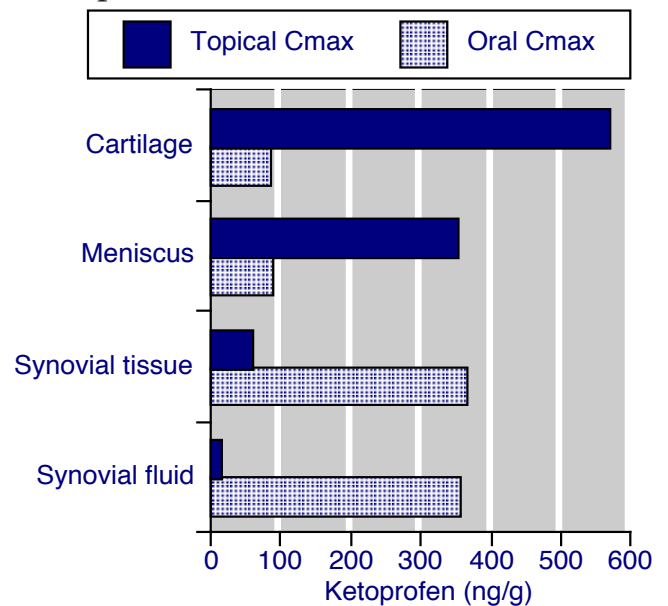


Figure 9: Comparison of median maximum concentrations of ketoprofen in joint tissue after topical and oral administration



Synovial tissue is highly vascularised and receives NSAID through the general circulation. It would be expected that, after the first few hours after a dose, both synovial tissue and fluid would have similar concentrations to plasma.

What is so interesting is that the different routes of administration give rise to completely different drug concentrations in joint tissue (Figure 9). Topical administration has higher concentrations in cartilage and meniscus, while oral administration has higher concentrations in synovial tissue and fluid. Topical administration produces high concentrations, usually in microgram per gram range, in some tissues. Concentrations are micromolar, easily high enough to inhibit cyclo-oxygenase enzymes, for which the concentration required for 50% inhibition is usually sub-micromolar, depending on assay conditions.

4 TOPICAL NSAIDS FOR STRAINS AND SPRAINS

Topical NSAIDs, either prescribed or bought without prescription, are often used for soft tissue injuries, or strains or sprains. This review sought evidence for their effectiveness in these conditions.

Clinical bottom line

Topical NSAID was significantly better than placebo in 19 of the 26 trials, with a pooled relative benefit of 1.6 (1.4 to 1.7), and NNT of 3.8 (3.4 to 4.4) compared with placebo for the outcome of half pain relief at seven days. Ketoprofen was significantly better than all other topical NSAIDs.

Local adverse events, systemic adverse events, or withdrawals due to an adverse event were rare, and no different between topical NSAID and placebo.

Background

The utility of topical NSAIDs has been questioned. This systematic review [12] updated a previous review [4] by accepting only higher quality trials (randomised, double blind), omitting salicylates, and adding newer trials.

Systematic review

The review sought studies in four electronic databases, reviews, and by writing to all companies worldwide marketing topical NSAIDs.

- Date review completed: April 2003
- Number of trials included: 24 placebo controlled, eight active controlled, four with both active and placebo controls.
- Number of patients: 2,853 in placebo controlled trials, 433 in active controlled trials had analysable data.
- Control groups: Placebo gel or cream, or oral NSAID.
- Main outcomes: Clinical success, representing approximately a 50% reduction in pain over seven days.

Results

The trials included were of high quality and validity. Quality scores were high, with 24/28 placebo controlled and 11/12 active controlled trials scoring 3 or more points out of a

maximum of 5. Validity scores were also high, with 25/28 placebo controlled and 10/12 active controlled trials scoring 9 or more out of a maximum of 16. These high scores minimised the possibility of bias.

Placebo controlled trials

Twenty-six trials with information from 2,853 patients were analysed for efficacy. In 19 of the 26 trials topical NSAID was significantly better than placebo. Topical NSAIDs as a class were significantly better than placebo (Table 1), with an NNT of 3.8 (3.4 to 4.4). There were 22/26 studies with higher quality and validity scores that minimised bias, and these also had an NNT of 3.8 (Table 7).

Efficacy estimates were also made for five individual drugs studied in at least three trials (Table 7). All were significantly better than placebo, but in the case of indomethacin just so. Ketoprofen had the lowest (best) NNT of 2.6 (2.2 to 3.3). The result for ketoprofen was significantly better than for ibuprofen, felbinac, piroxicam and indomethacin (Figure 10).

Topical compared with oral NSAIDs

Three trials, with 433 patients, compared a topical NSAID with an oral NSAID (indomethacin 75 mg daily in one trial and ibuprofen 1,200 mg daily in two). Overall rates of treatment success were similar for topical NSAID (57%) and oral NSAID (62%), with no statistically significant difference (relative benefit 0.9; 0.8 to 1.1).

Adverse events

There was no statistically significant difference between the numbers of patients experiencing one or more local adverse events (4%), one or more systemic adverse events (2.5%), or the numbers of patients withdrawing due to an adverse event (0.8%), with topical NSAIDs than with placebo (Table 7). Systemic adverse events and adverse event withdrawals did not differ between topical and oral NSAID.

Comment

Trials included in this review were of high quality and validity, so minimising the possibility of bias. The outcomes chosen were at one week, which is appropriate for soft tissue injuries, and for strains and sprains.

Figure 10: NNTs for individual topical NSAIDs (bars show 95% confidence interval)

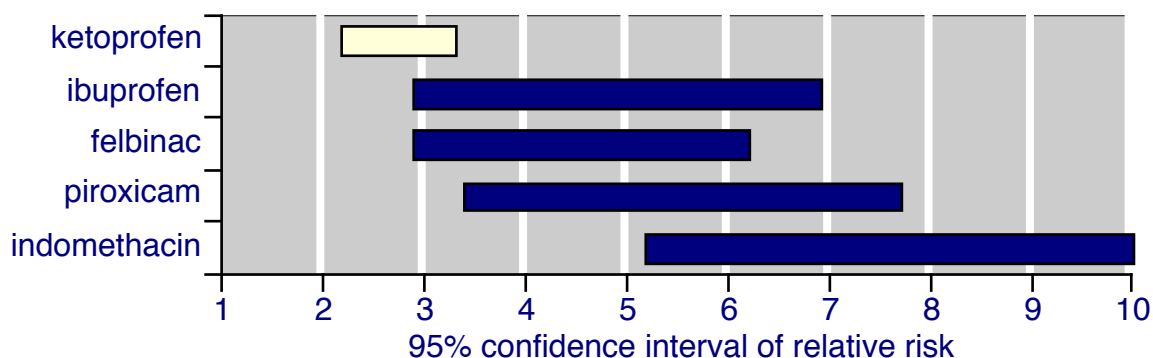


Table 7: Main results for topical NSAIDs in strains and sprains

Trials			Success with		Relative benefit (95% CI)	NNT (95% CI)
	Trials	Patients	Topical NSAID	Topical placebo		
All trials	26	2853	993/1531	512/1322	1.6 (1.4 to 1.7)	3.8 (3.4 to 4.4)
Quality ≥ 3 and validity ≥ 9	22	2511	876/1355	440/1156	1.6 (1.4 to 1.8)	3.8 (3.3 to 4.4)
Efficacy by topical NSAID						
ketoprofen	6	517	203/261	101/256	2.1 (1.7 to 2.5)	2.6 (2.2 to 3.3)
ibuprofen	5	365	112/183	67/182	2.0 (1.5 to 2.6)	4.1 (2.9 to 6.9)
felbinac	3	413	112/210	57/203	1.6 (1.2 to 2.2)	4.0 (2.9 to 6.2)
piroxicam	3	563	179/283	118/280	1.4 (1.1 to 1.7)	4.7 (3.4 to 7.7)
indomethacin	3	394	95/197	76/197	1.3 (0.99 to 1.6)	10 (5.2 to infinity)
Adverse events						NNH 95% CI
Local adverse events	23	2741	65/1464	60/1277	1.6 (1.0 to 2.5)	Not calculated
Systemic adverse events	23	2685	40/1437	30/1248	1.4 (0.9 to 2.0)	Not calculated
Adverse events withdrawals	24	3011	13/1601	10/1410	1.6 (0.8 to 3.4)	Not calculated

This systematic review confirms the results of a previous review. Topical NSAIDs are effective for pain relief in conditions like strains and sprains, using the outcome of at least half pain relief over seven days. These conditions are usually self-limiting, and with time get better by themselves, so over periods longer than a week less difference would be expected.

In limited studies topical NSAIDs were no different from standard doses of oral NSAID. Topical NSAIDs were not associated with any higher rate of adverse events, either local or systemic.

Of all the topical NSAIDs available, ketoprofen has the best (lowest) NNT, and was significantly better than others.

5 TOPICAL NSAIDS FOR CHRONIC MUSCULOSKELETAL PAIN

Topical NSAIDs are prescribed and used for chronic musculoskeletal conditions, though licensed indications vary from country to country. This review sought evidence for their effectiveness in these conditions.

Clinical bottom line

Topical NSAIDs were clearly better than placebo in chronic musculoskeletal pain, with an NNT of 4.4 (3.6 to 5.6) in the best trials. Studies were generally of short duration, and no single preparation could be shown to be better than another. No study showed oral NSAID to be better than topical NSAID.

Local adverse events, systemic adverse events, or withdrawals due to an adverse event were rare, and no different between topical NSAID and placebo.

Background

The utility of topical NSAIDs has been questioned. This systematic review [13] updated a previous review [4] by accepting only higher quality trials (randomised, double blind), omitting salicylates, and adding newer trials.

Systematic review

The review sought studies in four electronic databases, reviews, and by writing to all companies worldwide marketing topical NSAIDs.

- Date review completed: April 2003
- Number of trials included: 15 placebo controlled, seven active controlled, three with both active and placebo controls.
- Number of patients: 1,502 in placebo controlled trials, 764 in active controlled trials had analyzable data.
- Control groups: Placebo gel or cream, or oral NSAID.
- Main outcomes: Clinical success, representing approximately a 50% reduction in pain over 14 days.

Patients were generally over 40 years old, predominantly with musculoskeletal disorders, and with baseline pain of moderate to severe intensity.

Results

The trials included were of high quality and validity. Quality scores were high, with 16/18 placebo controlled and 9/10 active controlled trials scoring 3 or more points out of a maximum of 5. Validity scores were also high, with 14/18 placebo controlled and 8/10 active controlled trials scoring 9 or more out of a maximum of 16. Potential bias was therefore minimised.

Placebo controlled trials

Fourteen trials with information from 1,502 patients were analysed for efficacy. Topical NSAIDs as a class were significantly better than placebo (Table 8), with an NNT of 4.6 (3.8 to 5.9). There were 10 studies with higher quality and validity scores that minimised bias, and these also had an NNT of 4.4 (Table 8).

Adverse events

Eighteen placebo controlled trials (2,032 patients) provided some information on adverse events (Table 8). There was no statistically significant difference between topical NSAID and topical placebo for the number of patients experiencing local adverse events (6%), systemic adverse events (3%), or the number withdrawing due to an adverse event (1%). With topical NSAID or topical placebo, local adverse events were usually described as rash, itching or stinging, and were predominantly mild.

Topical compared with oral NSAIDs

Three trials, with 764 patients, compared a topical NSAID with an oral NSAID (diclofenac 100 mg daily in one trial and ibuprofen 1,200 mg daily in two). Overall rates of treatment success were similar for topical NSAID (37%) and oral NSAID (37%), with no statistically significant difference (relative benefit 1.1; 0.9 to 1.3).

Adverse events

Eight of the active controlled trials (1,461 patients) provided some information on adverse events (Table 8). In two active

controlled trials comparing topical with oral NSAID, local adverse events occurred more frequently (8%) with topical than with oral NSAID (3%). Systemic adverse events and adverse event withdrawals did not differ between topical and oral NSAID.

Comment

Trials included in this review were of high quality and validity, so minimising the possibility of bias. The outcomes chosen were at two weeks. For chronic musculoskeletal conditions, longer duration trials (12 weeks or more) would be more appropriate.

Topical NSAIDs were clearly better than placebo in chronic musculoskeletal pain. There was a limitation of study duration, which was generally of two weeks or so. There was insufficient information on different topical NSAID preparations to tell whether any one topical NSAID was better than another.

In limited studies topical NSAIDs were no different from standard doses of oral NSAID. Topical NSAIDs were not associated with any higher rate of adverse events, either local or systemic.

Another view of of the same topic

Another review of topical NSAIDs in musculoskeletal pain [14] was published in 2004. It concluded that there was no evidence of superior efficacy beyond two weeks of use. It is worth looking at how this conclusion was reached.

Table 8: Main results for topical NSAIDs in chronic pain (NNH not calculated for adverse events because there was no significant difference)

Trial characteristic	Number of		Success/total		RB (95% CI)	NNT (95% CI)
	Trials	Patients	Treatment	Placebo		
All trials	14	1502	371/771	193/731	1.9 (1.7 to 2.2)	4.6 (3.8 to 5.9)
Validity ≥ 9 and quality ≥ 3	10	1197	247/622	98/575	2.4 (2.0 to 3.0)	4.4 (3.6 to 5.6)
Condition						
knee osteoarthritis	5	567	127/307	58/260	2.0 (1.6 to 2.6)	5.3 (3.8 to 8.6)
other musculoskeletal	9	935	244/464	135/471	1.9 (1.6 to 2.2)	4.2 (3.3 to 5.6)
Placebo controlled trials						
Type of adverse event	Trials	Patients	Event with topical	Event with placebo	RR (95% CI)	
Local adverse events	15	1734	53/949	48/785	1.0 (0.7 to 1.4)	
Systemic adverse events	16	1838	33/1002	14/836	1.7 (0.96 to 2.9)	
Withdrawals from adverse events	10	1225	10/697	7/528	0.9 (0.4 to 2.1)	
Active controlled trials: topical vs oral						
Type of adverse event	Trials	Patients	Event with topical	Event with oral	RR (95% CI)	
Local adverse events	2	443	19/243	4/118	3.0 (1.1 to 8.5)	
Systemic adverse events	3	764	82/408	87/356	0.8 (0.6 to 1.1)	
Withdrawals from adverse events	3	764	19/408	24/356	0.7 (0.4 to 1.3)	

1. Four studies included in the meta-analysis used topical salicylates, which are not now classified as NSAIDs.
2. Outcomes are converted to effect sizes for reporting. This gives an overall smoothed out average result but can allow different outcomes to be pooled, and pooling means where there is probably a skewed distribution can be a problem.
3. Clinical response is defined as at least moderate or excellent or 50% reduction in pain or improvement in symptoms. After removing trials that used salicylates, for comparisons against placebo only one trial provides data for analysis at one week, one trial at two weeks, and no trials at three or four weeks. Similarly for comparison of topical vs oral NSAID, only one trial provides data at four weeks, and shows no difference between topical and oral preparations for this outcome.
4. One paper (Ottillinger) appears as three trials in one of the figures. It is actually three doses of eltenac (0.1, 0.3, 1.0%) vs placebo. it is not sensible to treat the individual arms of the trial as separate comparable trials.
5. Eltenac, even the highest dose does not show significant benefit over placebo, at two trials that used it.
5. Eltenac had no effect at one week, two weeks, three weeks or four weeks. Eltenac is the only topical NSAID tested beyond two weeks in the review.
6. In August 2004 a large (248 patient) randomised trial of topical diclofenac and placebo for four weeks in patients with osteoarthritis of the knee was published [15]. Statistical benefit over placebo was found for pain, physical function, stiffness, pain on walking, and global assessment.
7. Other large and long duration studies showing long-term efficacy of topical NSAIDs in osteoarthritis are due to be published in 2004.

6 SAFETY OF TOPICAL NSAIDS

Randomised trials can give useful information about common adverse events, which are usually mild and reversible. Rare, serious, and often irreversible, adverse events are often better studied in observational studies.

Clinical bottom line

When other drug use is taken into account there was no hint of association between topical NSAIDs and upper gastrointestinal bleeding. Despite limitations of this sort of study, the evidence is that topical NSAIDs do not cause gastrointestinal problems.

Study

This study [16] covered 320,000 people living in Tayside, Scotland between 1989 and 1994. A case was any patient with a diagnostic code for upper gastrointestinal bleeding and perforation. This included acute, chronic or unspecified gastric ulcer, duodenal ulcer, with haemorrhage or perforation, or haematemesis or melena. Accuracy was determined in a validation study.

Controls were from the community or hospital. Community controls were matched for age and sex and were generated randomly for each case (up to six controls for each case).

Up to two hospital controls were also selected, matched for age and sex, and generated randomly for each case. They could have been admitted to hospital for any reason other than gastrointestinal bleeding and perforation.

Previous exposure to any oral and topical NSAIDs, and gastrointestinal healing drugs, was examined for association with admission for GI bleeding. Topical NSAID had a wide definition that also included rubefacients (salicylates).

Results

Over four years, 23,100 patients had been prescribed topical NSAIDs (7% of the population).

There were 1101 cases and 6593 controls. Association with exposure was assessed for 45-day and ever exposure, with community and hospital controls, and for all cases, bleeding and perforation separately, and with both crude odds ratios and odds ratios calculated using conditional logistic regression.

Oral NSAIDs, topical NSAIDs and ulcer healing drugs were always significantly associated with higher bleeding rates than community controls, without any adjustment for use of other drugs (Table 9). Oral NSAIDs and ulcer healing drugs, but not topical NSAIDs were associated with higher bleeding rates than hospital controls without any adjustment.

The picture changes when adjustment is made for the use of other drugs using conditional logistic regression:

- ◆ Oral NSAIDs were significantly associated with higher bleeding rates irrespective of controls used, or duration of exposure.
- ◆ Topical NSAIDs were never significantly associated with higher bleeding rates irrespective of controls used, or duration of exposure.
- ◆ Ulcer healing drugs were predominantly significantly associated with higher bleeding rates.

Comment

The problem with examining safety of topical NSAIDs is that patients may well have used oral NSAIDs, or be also using oral NSAIDs, and may be using topical NSAIDs because

Table 9: Association between drug use and GI bleeding, no adjustment for other drug use compared with community or hospital controls (shaded areas show statistical significance)

Drug	Exposure	Crude odds ratios	
		Community	Hospital
Oral NSAID	45-day	2.8	2.0
	Ever	1.5	1.0
Topical NSAID	45-day	2.6	1.6
	Ever	1.5	1.0
Ulcer healing	45-day	4.6	1.9
	Ever	4.3	1.8

they are at high risk of bleeding, and may therefore be taking ulcer-healing drugs. This complicates matters when looking for simple association between drug use and bleeding.

In this study, for instance, use of ulcer healing drugs was associated with higher rates of gastrointestinal bleeding. Yet we would not take this as evidence that ulcer healing drugs cause gastrointestinal bleeding, rather that people take these drugs because they are at higher risk of bleeding, and the use of ulcer healing drugs does not completely remove this risk.

So we have to take other criteria into account. When this is done, the association of oral NSAIDs with bleeding remains. But for topical NSAIDs, there was no hint of association. Despite limitations of this sort of study, the evidence is that topical NSAIDs do not cause gastrointestinal problems.

Other types of adverse event can occur, though rarely. One is photosensitivity to topical NSAIDs, dealt with in a later section.

7 PHOTSENSITIVITY TO TOPICAL NSAIDs

Clinical bottom line

Photoallergic reactions to topical NSAIDs are rare, seem to be most prominent with ketoprofen, and occur at about 1-2 cases per 10,000.

Background

All NSAIDs could potentially induce phototoxic reactions. The main NSAID with known phototoxic adverse reactions is ketoprofen, which can undergo UV-catalysed chemical changes that render toxic reactions more likely. On irradiation photosensitisers can be transformed into haptens with a benzophenone moiety, leading to an immune response after binding to a tissue antigen. These sensitivity reactions usually regress after discontinuation of the drug, but can occasionally be prolonged [17].

Review

The review [18] collects a number of case reports of photocontact dermatitis after application with topical ketoprofen amounting to about 100 patients, as well as epidemiological data from Italy, France and Sweden. The best estimate of rate is 1-2 per 10,000 patients treated.

Comment

Photoallergic reactions to topical NSAIDs are rare, seem to be most prominent with ketoprofen, and occur at about 1-2 cases per 10,000.

8 HEALTH ECONOMICS OF TOPICAL NSAIDs

Clinical bottom line

The use of topical NSAIDs in patients in whom it is appropriate probably costs less than using oral NSAIDs. Although the acquisition cost of topical NSAIDs tends to be higher than that of generic oral NSAIDs, lower costs of adverse events result in savings for the whole health economy.

Background

Topical NSAID use is sometimes questioned because they cost more than generic oral NSAIDs. But oral NSAIDs are associated with significant adverse events (gastrointestinal, heart failure, and renal failure). Topical NSAIDs have much lower plasma concentrations, and are not associated with higher rates of adverse events, or at any rate of gastrointestinal adverse events.

Survey

Bandolier sought studies of the health economics of topical NSAID use by searching PubMed. None were found in the last five years (1999 on), and only two previously.

Results

The two studies found are summarised in Table 10. Both compared a topical NSAID with an oral NSAID (generic ibuprofen), and examined costs over one month and three months. Both used literature information about rate and costs of upper gastrointestinal adverse events. Neither considered any additional benefits relating to lower rates of cardiovascular or renal adverse events, or anaemia associated with oral NSAID use.

Both studies concluded that total costs of topical NSAID were lower than those of oral NSAIDs, and for the same reason, because of lower adverse event rates. Higher acquisition costs for topical NSAID were offset by lower adverse event costs.

Comparison with oral NSAIDs

Oral NSAIDs are known to cause gastrointestinal bleeding [19], renal failure [20, 21], and congestive cardiac failure [22, 23]. Table 11 puts all this into the perspective of an average UK population of 100,000 [24], where 3,800 over 65s use NSAIDs regularly. Of this 3,800 there would be 18 hospital admissions every year for upper gastrointestinal bleeding, 10 for acute renal failure and 22 for congestive heart failure. These latter seem high, but in both cases the bulk of the events would be in those aged 75 and over.

For both renal failure and CHF NSAIDs seem to uncover incipient disease. For renal failure there are several, smaller, confirmatory studies, and for CHF at least one [23]. For both there appears to be a plausible mechanism, dose-response relationships, and particular association with NSAIDs with longer half-lives. Renal failure has a high mortality, and CHF

Table 10: Summary of health economic studies on topical NSAIDs

Reference	Description	Results
Peacock & Rapier. Br J Med Econ 1993 6: 135-142	Cost-effectiveness study of one month treatment of 1,000 patients with oral ibuprofen, Arthrotec, or topical felbinac. Study included drug costs and cost of	Cost per 1,000 patients was: oral ibuprofen £41,408 oral Arthrotec £17,924 topical felbinac £7,319
McKell & Steward. Br J Med Econ 1994 7: 137-146	Cost minimisation analysis comparing oral ibuprofen (1200 mg daily) with topical piroxicam (three times daily) in mild OA.	Cost of three months' treatment: oral ibuprofen £89 topical piroxicam £55

is also serious, as treatment is unlikely to restore patients' functioning to previous levels.

The good news is that for most older patients sensible assessment and pertinent guidance should mean that many of these events could be avoided. While the new coxibs are not associated with elevated risks of gastrointestinal bleeding, there is no evidence, or indeed likelihood, that they will not precipitate renal failure or CHF.

Put in a humanitarian and economic context, these 50 first hospital admissions a year (Table 11) per 100,000 population are equivalent to 30,000 admissions a year in the UK. Most are avoidable. Information we have suggests an average stay of about a week, costing about £1,400 each. That's something like £40 to £50 million a year for the NHS.

Gastrointestinal bleeding is more expensive than these hospital costs alone, of course. Adding in other costs, like use of acid suppressant prophylaxis, suggests that the overall cost of that adverse event alone to the NHS was £250 million some years ago [25].

Comment

There is very considerable evidence that oral NSAIDs produce significant upper gastrointestinal adverse events because of gastroduodenal ulceration, and, in some cases, bleeding. These require hospital treatment or prophylaxis with proton pump inhibitors to prevent these adverse events. Gastrointestinal adverse events are known not to be a feature of topical NSAID use.

That topical NSAID use would be cheaper than oral NSAID use, in patients for whom topical NSAIDs would be appropriate, makes sense. The arguments are similar to those made for the cyclooxygenase-2 inhibitors, and recent research has shown that overall costs of these newer drugs are no more than oral NSAIDs [26], again because higher acquisition costs are offset by savings elsewhere.

Table 11: NSAID adverse effects in an older population of an average UK structure

Event	Cases per year
Upper GI bleed	18
Acute renal failure	10
Congestive heart failure	22

Information based on an average 100,000 patients where 3,800 over 65s take NSAIDs

With topical NSAIDs plasma concentrations are very considerably lower than after oral use. This probably explains the lack of serious gastrointestinal adverse events with topical NSAIDs. It would be reasonable to suppose that topical NSAIDs should have lower rates of renal failure and congestive heart failure than oral NSAIDs, but we do not know this from available evidence.

The argument is strengthening that topical NSAIDs are likely to be safe to use in patients for whom oral NSAIDs are not safe. This could be a significant proportion of the older elderly population.

That safety argument is also a cost argument. Oral NSAIDs may be relatively cheap, but their severe adverse events are not. There is a significant economic argument as well as humanitarian argument to be developed here.

What patients want

In a study 100 consecutive patients living in the community with osteoarthritis of the knee, preference data on treatment choices and utilities were collected using conjoint analysis [27]. Patients were given information about treatment efficacy, common adverse events, route and frequency of administration, onset of action and risk of ulcer for five treatments: nonselective NSAIDs, coxibs, opioids, glucosamine (all oral), and capsaicin cream.

The average age of the 100 patients was 70 years, and 80% were women. Half had a current health status of fair or worse, a third had had dyspepsia from nonselective NSAIDs, 22% had a previous ulcer and 5% had been admitted to hospital for gastrointestinal bleeding. Most of them were using or had used nonselective NSAIDs, coxibs, glucosamine and analgesic creams, but only a third had previously used opioid preparations. They were therefore experienced patients.

Patient preference for treatment where they paid a monthly co-payment (\$10 per month for NSAIDs, coxibs, and opioid preparations; \$25 per month for glucosamine or capsaicin) was for capsaicin (34%), and none preferred NSAIDs. Decreasing the risk of ulcers made little difference, but increasing the efficacy of nonselective NSAIDs of coxibs to 75% of patients benefiting from 50% benefiting changed choices so that coxibs became the first choice. Much the same results occurred when patients paid the full cost of their medicines. Patients with health status rated by them as fair or worse were less likely to choose capsaicin (26%) than those who felt well or very well (56%).

TOPICAL ANALGESICS SUMMARY

We have four systematic reviews of topical analgesics (rubefaciants, capsaicin, and NSAIDs) in the treatment of acute and chronic painful conditions in adults. There are limitations with any systematic review and meta-analysis, which can only be as good as the original trials. The trials often span several decades, and contemporary examination finds fault with them in several respects:

- ◆ Trials are often small. Small size can lead to the influence of chance effects on treatment and placebo event rates, and individual trial results will often provide unreliable estimates of the magnitude of any effect.
- ◆ It is frequently the case that for any particular topical agent, different preparations are used, with different application schedules, different concentrations of active agent, in different formulations. This leads to an obvious degree of clinical heterogeneity, even when patients, trial design, outcome, and duration are otherwise the same.
- ◆ Outcomes in the trials are not consistent, and a hierarchy of outcomes had to be constructed to allow the meta-analysis. The same hierarchy was used in all four reviews.
- ◆ Duration of trials in acute conditions like strains and sprains usually covered one or two weeks when resolution is likely to occur even in the absence of treatment. Using outcomes at one week is therefore appropriate. For chronic painful conditions, like arthritis or neuropathic pain, where the duration of the condition is months or (more probably) years, trials with a two-week duration are inadequate. In the era of cyclooxygenase-2-specific-inhibitors we have grown accustomed to trials of 12 weeks to one year. Before that time, trials of oral NSAIDs were also short and small. However, trials of cyclooxygenase-2-specific-inhibitors also show that, for oral NSAIDs, outcomes at two and 52 weeks are consistent, and change little over time.
- ◆ One implication of short duration studies is that they will not capture important long-term safety information. This may be important for ongoing applications of gels, creams or sprays. We have other information

that indicates that topical NSAIDs do not cause the gastrointestinal harm found with oral NSAIDs, nor are they associated with increased renal failure.

These limitations are important. The evidence should be re-considered for chronic conditions when several large (600+ patients) comparisons of topical NSAIDs with oral NSAIDs have reported. These newer trials, being larger, longer, and with (one hopes) better-designed outcomes, will be important in confirming the results of the meta-analysis.

Comment

Table 12 summarises the main results from placebo-controlled trials for the topical analgesics.

In acute conditions, the low NNT for topical NSAIDs shows them to be effective. This evidence is robust, because the trials were of sufficient quality to avoid bias, they were valid, and there was a considerable amount of information from 2,800 patients. Ketoprofen, in particular, with a NNT of 2.7, was highly effective. In acute pain studies, effective analgesics have NNT values of 2-5.

There is inadequate data to make a robust conclusion that rubefaciants had any efficacy at all. Though the NNT was low, it was derived only from 182 patients, and the three best trials showed no effect. Unless more trial information becomes available, rubefaciants are best regarded as being without efficacy.

In chronic conditions the major problems were limited amount of data and limited durations of trials. There is inadequate data to make a robust conclusion about the efficacy of capsaicin in musculoskeletal conditions because the number of patients in whom it was tested was limited, and because of the poor estimate of efficacy from those trials. The evidence that we have suggests that topical capsaicin is less effective than antidepressants and anticonvulsants in neuropathic pain, with NNTs of about 3 compared with placebo at three to six months (Table 13).

The NNT of about 5 in chronic musculoskeletal conditions might be compared with those of about 3 for NSAIDs in

Table 12: Summary of results from meta-analyses of placebo-controlled trials

Treatment	Acute conditions		Chronic conditions	
	number of trials (patients)	NNT (95%CI)	number of trials (patients)	NNT (95%CI)
Rubefacient	3 (182)	2.1 (1.7 to 2.8)	6 (429)	5.3 (3.6 to 10)
Capsaicin neuropathic	no data		6 (656)	5.7 (4.0 to 10)
Capsaicin musculoskeletal	no data		3 (368)	8.1 (4.6 to 34)
Topical NSAID	26 (2853)	3.8 (3.4 to 4.4)	14 (1502)	4.6 (3.8 to 5.9)

Duration: Acute pain 7 days, chronic pain 14 days, except capsaicin which was 8 weeks
 Comparator: placebo preparations rubbed on in same way as active

Table 13: Summary of results from meta-analyses of placebo-controlled trials in chronic painful conditions

Treatment	Condition	NNT
NSAID	Dysmenorrhoea	2-4
Coxib	Dysmenorrhoea	3
Antidepressants	Diabetic neuropathy or post-herpetic neuralgia	3
Anticonvulsants	Diabetic neuropathy or post-herpetic neuralgia	3
Antidepressants	Fibromyalgia	4
Glucosamine	Osteoarthritis	5
Avocado/soybean unsaponifiables	Osteoarthritis	4
Topical NSAID	Musculoskeletal, mainly OA	5
Capsaicin	Musculoskeletal, mainly OA	6
Capsaicin	Neuropathic pain	8

TOPICAL NSAIDS FOR OA: UPDATE END 2004

The year 2004 saw an upsurge of publications on topical NSAIDs, with three recent systematic reviews and several new randomised trials. The randomised trials were larger and longer, and in patients with arthritis, and with up-to-date outcome and reporting criteria. The current state of knowledge has been summed up on the new Bandolier Internet section on topical analgesics, but briefly for topical NSAIDs it comes down to the following:

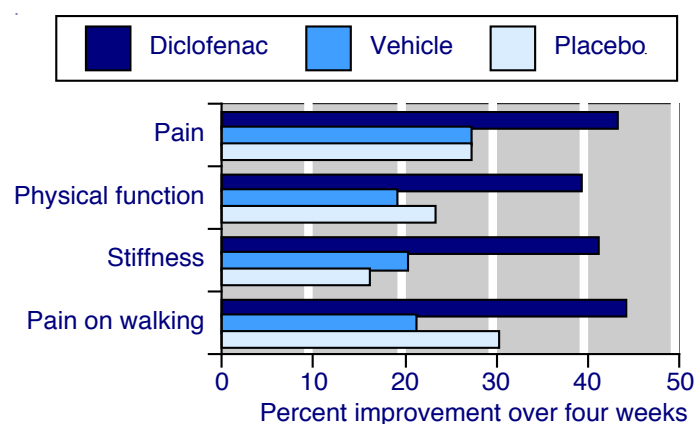
- Topical NSAIDs can penetrate skin and underlying tissues, with ketoprofen and diclofenac amongst the most likely to be effective based on laboratory experiments.
- Topical NSAIDs are found in high concentration in the knee joint (particularly meniscus and cartilage).
- Topical NSAIDs produce much lower plasma concentrations than oral NSAIDs, typically 5% of oral concentrations or less.
- In strains and sprains over seven days, topical ketoprofen is probably better than other topical NSAIDs, and topical indomethacin is not significantly better than placebo.
- In chronic musculoskeletal pains, topical NSAIDs are better than placebo at two weeks, but confidence is limited by the short duration of trials.

The main unknown is in chronic conditions, where larger, longer trials have been needed to give confidence in longer-term efficacy of topical NSAIDs. In particular, direct comparison of the same NSAID in topical and oral formats has been missing. We now have three large randomised trials against placebo and oral NSAID that increase confidence.

Placebo control, 4 weeks [27]

This trial was properly randomised (independent computer-generated allocation), with concealed allocation, and identical controls to maintain blinding. Patients had primary osteoarthritis in at least one knee verified radiologically within the previous six months, at least moderate pain, and aged 18 to 80 years. There were sensible exclusion criteria such as use of oral NSAIDs. Assessments were made at baseline and after four weeks, and the trial outcomes accorded with those of the latest advice on trials in arthritis.

Figure 11: Results of four-week comparison of topical diclofenac with vehicle and placebo



Three topical treatments were tested: topical diclofenac in dimethylsulphoxide (DMSO), DMSO without diclofenac (vehicle), and a placebo without either diclofenac and with a low concentration of DMSO. A monitored amount of solution was applied to the knee being treated in a standard way, without rubbing, four times daily.

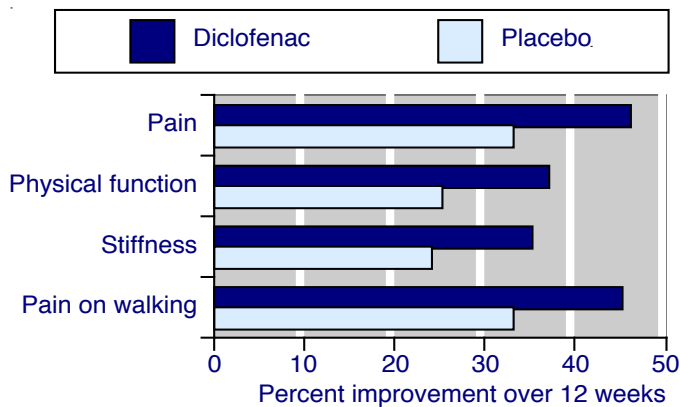
Results

There were 248 patients in the three groups, and the groups were well matched at baseline, being about 60% women with an average age of about 62 years. Almost 90% completed the four weeks of treatment. The main reasons for withdrawal were lack of effect in vehicle and placebo groups (8/80 and 10/84 respectively), and adverse events with topical diclofenac (5/84) and vehicle (3/80).

WOMAC scores for pain, physical functioning, stiffness, and pain on walking all fell significantly more with topical diclofenac than vehicle or placebo (Figure 11). Patient global assessment was significantly better with topical diclofenac than vehicle or placebo.

Dry skin (36%) and rash (11%) were more frequent with topical diclofenac than vehicle or placebo. There was no difference in gastrointestinal or other adverse events.

Figure 12: Results of 12-week comparison of topical diclofenac and placebo



Placebo control, 12 weeks [28]

The basic design features of this trial were as for the four-week study, with efficacy measured after 12 weeks. A monitored amount of solution containing diclofenac or vehicle placebo control identical but without diclofenac was applied to the knee being treated in a standard way without rubbing, four times daily.

Results

Randomisation involved 326 patients, and treatment and placebo groups were well matched at baseline, being about 68% women with a mean age of 64 years. With placebo and topical diclofenac the main reason for withdrawal was lack of efficacy (42/162; 26% and 28/164; 17% respectively). Adverse event withdrawals were rare (4/162 and 8/164 respectively).

WOMAC scores for pain, physical functioning, stiffness, and pain on walking all fell significantly more with topical diclofenac than vehicle placebo control (Figure 12). Patient global assessment was significantly better with topical diclofenac than vehicle placebo control.

Local adverse reactions of dry skin and rash occurred more frequently with topical diclofenac than with vehicle control (37% vs 25% and 11% vs 5% respectively). Gastrointestinal adverse events were rare and occurred no more frequently with topical diclofenac than with placebo.

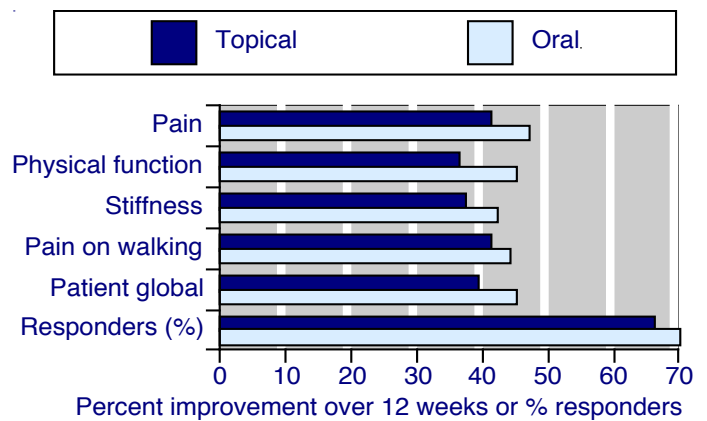
Oral control, 12 weeks [29]

The basic design features of the third study were similar to the placebo-controlled trials, except that here the design was double-dummy, with oral diclofenac 150 mg daily or oral placebo and topical diclofenac or topical placebo arranged so that topical and oral diclofenac were directly compared. Topical or oral diclofenac were used three times daily for 12 weeks, and only one knee, that with the highest pain score at baseline, was used for efficacy measurement.

Results

The 622 patients randomised had an average age of 64 years and 58% were women. The two groups were well matched at baseline. Sixty-one percent completed the 12 weeks. Of

Figure 13: Results of 12-week comparison of topical and oral diclofenac



those withdrawing, adverse events contributed 20% with topical and 25% with oral diclofenac, while lack of efficacy contributed 9% and 3% respectively.

WOMAC scores for pain, physical functioning, stiffness, pain on walking, patient global assessment, and number of responders were similar with topical and oral diclofenac (Figure 13) using an intention to treat analysis, or a per protocol analysis. A responder was defined as a patient with a 50% or greater improvement in pain or function that was 20 mm or more on a 100 mm VAS, or 20% or greater improvement in at least two of pain, function, or patient global assessment that was 10 mm or more on a 100 mm VAS.

Application site reactions occurred almost uniquely in patients using active topical diclofenac. Dry skin (27%), rash (12%), and pruritus (6%) were most common. Gastrointestinal adverse events occurred in both groups, but with oral diclofenac they occurred significantly more often for dyspepsia, abdominal pain and diarrhoea (Table 14). These gastrointestinal adverse events were also more likely to be severe with oral than topical diclofenac (Table 14). Overall, the number needed to harm (NNH) for severe dyspepsia, abdominal pain or diarrhoea for oral compared with topical diclofenac for 12 weeks was 11 (95% CI 8 to 19). Asthma, dyspnoea and dizziness occurred infrequently, but more commonly with oral diclofenac, while pharyngitis was infrequent and more common with topical diclofenac.

Laboratory changes were also more common for oral compared with topical diclofenac (Table 15). Elevations in liver enzymes and reduced haemoglobin gave NNH values of 7 to 14 (Table 15). Clinically significant elevations of three times the upper limit of normal or more occurred more frequently with oral diclofenac (1%, 5% and 4% with AST, ALT and GGT) than topical diclofenac (0.4%, 1.1% and 1.4% respectively).

Comment

These are important milestones in our thinking about the evidence for topical NSAIDs in chronic painful conditions like osteoarthritis of the knee. They provide better evidence that topical NSAID is better than placebo, and augment shorter studies showing that topical and oral NSAIDs have equivalent efficacy. There is substantially more evidence that topical NSAIDs do less harm than oral NSAIDs.

Table 1: Adverse events over 12 weeks with topical and oral diclofenac

Adverse event	Number (%) with		Relative risk (95% CI)	NNH (95% CI)
	Topical diclofenac (311)	Oral diclofenac (311)		
All reported				
Dyspepsia	48 (15)	81 (26)	0.6 (0.4 to 0.8)	9 (6 to 23)
Abdominal pain	36 (12)	67 (22)	0.5 (0.4 to 0.8)	10 (6 to 24)
Diarrhoea	27 (9)	54 (17)	0.5 (0.3 to 0.8)	12 (7 to 29)
Severe				
Dyspepsia	2 (0.6)	11 (3.5)	0.2 (0.04 to 0.8)	35 (19 to 152)
Abdominal pain	2 (0.6)	13 (4.2)	0.2 (0.03 to 0.7)	28 (17 to 88)
Diarrhoea	1 (0.3)	9 (2.9)	0.1 (0.01 to 0.9)	39 (22 to 165)
All severe	5 (1.6)	33 (11)	1.2 (0.06 to 0.4)	11 (8 to 19)

Table 2: Laboratory adverse events with topical and oral diclofenac

Adverse event	Number (%) with		Relative risk (95% CI)	NNH (95% CI)
	Topical diclofenac (182)	Oral diclofenac (195)		
Elevated AST	1 (0.5)	15 (7.7)	0.1 (0.01 to 0.5)	14 (9 to 31)
Elevated ALT	5 (2.7)	35 (18)	0.2 (0.06 to 1.4)	7 (5 to 11)
Elevated GGT	8 (4.4)	31 (16)	0.3 (0.1 to 0.6)	9 (6 to 18)
Reduced haemoglobin	5 (2.7)	23 (12)	0.2 (0.1 to 0.6)	11 (7 to 25)
Reduced creatinine clearance	7 (3.8)	17 (8.7)	0.4 (0.2 to 1.04)	

The studies were performed impeccably and were large. They were properly randomised and blinded, and used outcomes recommended by the latest trial guidelines in osteoarthritis. They paid proper attention to adverse events. If there is a problem, it may be a question of formulation. The DMSO vehicle together with the diclofenac led to many local adverse events, probably more so than seen typically with gels, creams, or sprays.

And it is the adverse effects that are so important. Concentrating on them gives us a better insight into what happens with oral diclofenac, a frequently used NSAID. By now we have become used to the gastrointestinal adverse events, but it is still interesting to see the high rate of 10% of reduced haemoglobin with oral diclofenac, as well as the common elevations in liver enzymes and reduced creatinine clearance.

With doubts about the efficacy of paracetamol in osteoarthritis (Bandolier 128), and concerns about cardiovascular effects of oral coxibs that remain to be fully elucidated, guidelines on treatment will have to be revisited. The growing evidence of efficacy and safety with topical NSAIDs should become part of that process.

What's missing?

There are not now many gaps in our knowledge we need to be filled. Some might include

- 1 Studies of different topical NSAIDs in longer term studies in arthritis.
- 2 Observational studies looking at adverse events like renal and cardiac failure would be useful, especially as they would be predicted to show less harm from using topical compared with oral NSAID. This would buttress arguments for using topical NSAIDs, and help devise sensible care pathways, especially in early disease.
- 3 We need better help to know which patient to treat with which therapy. Logic would dictate that persons with single joint problems would be better served by topical rather than oral NSAIDs, but more robust evidence would be welcomed.
- 4 Perhaps a little more in the way of pragmatic trials about management, especially in primary care, and especially about combining therapies to maximise benefit and minimise harm.

REFERENCES

1. L Mason, RA Moore, S Derry, JE Edwards, HJ McQuay. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* 2004 328: 991-994.
2. WY Zhang, A Li Wan Po. The effectiveness of topically applied capsaicin. A meta-analysis. *European Journal of Clinical Pharmacology* 1994 46: 517-22.
3. L Mason, RA Moore, S Derry, JE Edwards, HJ McQuay, PJ Wiffen. Systematic review of efficacy of topical rubefacients containing salicylates for the treatment of acute and chronic pain. *BMJ* 2004 328: 995-998.
4. RA Moore et al. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *BMJ* 1998 316: 333-338.
5. KB Sloan, S Wasdo. Designing for topical delivery: prodrugs can make the difference. *Medicinal Research Reviews* 2003 23: 763-793.
6. JA Cordero et al. In vitro based index of topical anti-inflammatory activity to compare a series of NSAIDs. *European Journal of Pharmaceutics and Biopharmaceutics* 2001 51: 135-142.
7. C Rolf et al. Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. *Rheumatology* 1999 38: 564-567.
8. CA Heyneman et al. Oral versus topical NSAIDs in rheumatic diseases. A comparison. *Drugs* 2000 60: 555-574.
9. J Radermacher et al. Diclofenac concentrations in synovial fluid and plasma after cutaneous application in inflammatory and degenerative joint disease. *British Journal of Clinical Pharmacology* 1991 31: 537-541.
10. Anon. Brufen. Experimental, technical and clinical aspects of Brufen. The Boots Company plc, Nottingham, England (monograph).
11. WJ Wallis, PA Simkin. Antirheumatic drug concentrations in human synovial fluid and synovial tissue. *Clinical Pharmacology* 1983 8: 496-522.
12. L Mason et al. Topical NSAIDs for acute pain: a meta-analysis. *BMC Family Practice* 2004 5:10 (<http://www.biomedcentral.com/1471-2296/5/10>)
13. L Mason et al. Topical NSAIDs for chronic musculoskeletal pain. *BMC Musculoskeletal Disorders* 2004 5:28 (<http://www.biomedcentral.com/1471-2474/5/28>)
14. J Lin et al. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ* 2004 329: 324-330.
15. AA Bookman et al. Effect of topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. *Canadian Medical Association Journal* 2004 171: 333-338.
16. JM Evans et al. Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation: a record linkage case-control study. *BMJ* 1995 311: 22-26.
17. B Albès et al. Prolonged photosensitivity following contact photoallergy to ketoprofen. *Dermatology* 2000 201: 171-174.
18. H Bagheri et al. Photosensitivity to ketoprofen. Mechanisms and pharmacoepidemiological data. *Drug Safety* 2000 22: 339-349.
19. S Hernández-Díaz, LA García Rodríguez. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding and perforation: An overview of epidemiological studies published in the 1990s. *Archives of Internal Medicine* 2000 160: 2093-2099.
20. MR Griffin, A Yared, WA Ray. Nonsteroidal anti-inflammatory drugs and acute renal failure in elderly persons. *American Journal of Epidemiology* 2000 151:488-496.
21. D Henry et al. Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects. Results of a case-control study. *British Journal of Clinical Pharmacology* 1997 44: 85-90.
22. J Page, D Henry. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: An underrecognized public health problem. *Archives of Internal Medicine* 2000 160:777-784.
23. ER Heerdink et al. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. *Archives of Internal Medicine* 1998 158:1108-1112.
24. AL Blower, A Brooks, CG Fenn et al. Emergency admissions for upper gastrointestinal disease and their relation to NSAID use. *Alimentary Pharmacology and Therapeutics* 1997 11: 283-91.
25. RA Moore, CJ Phillips. Cost of NSAID adverse effects to the UK National Health Service. *Journal of Medical Economics* 1999 2: 45-55.
26. C Harley, S Wagner. Persistence with COX-2 inhibitors in managed care: an analysis of claims data. *Managed Care Interface* 2003 October 38-45.
27. AA Bookman et al. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled study. *Canadian Medical Association Journal* 2004 171: 333-338.
28. SH Roth, JZ Shainhouse. Efficacy and safety of a topical diclofenac solution (Pennsaid) in the treatment of primary osteoarthritis of the knee. *Archives of Internal Medicine* 2004 164: 2017-2023.
29. PS Tugwell et al. Equivalence study of a topical diclofenac solution (PENNSAID) compared with oral diclofenac in the symptomatic treatment of osteoarthritis of the knee: a randomized controlled study. *Journal of Rheumatology* 2004 31: 2002-2012.